1,2,4,5-Tetrachlorobenzene

CAS #95-94-3
Swiss CD-1 mice, at 0.0, 280, 720, and 1800 ppm in feed
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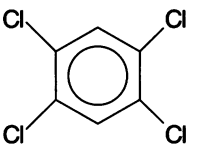

1,2,4,5-Tetrachlorobenzene (TCB), widely used as a chemical intermediate, was tested for its reproductive effects in Swiss CD-1 mice. TCB is a metabolic product of various chlorinated aromatics and is part of a class of halobenzene compounds with a long biologic half-life. This study was conducted to produce some public-domain information and to pursue some initial data generated in a 90-day toxicity study. That study found significant adverse effects on female cyclicity in B6C3F1 mice. Data from that 90-day study and from a 2-week dose-range-finding study (Task 1) were used to set exposure concentrations for the Task 2 continuous cohabitation study just slightly below those used in the 90-day study: 280, 720, and 1800 ppm in the feed. The reduction reflected an attempt to account for the systemic toxicity of TCB and the anticipated distributional changes that would likely occur during pregnancy and lactation. These concentrations produced average estimated daily intakes of TCB approximately 40, 100, and 250 mg/kg/day.

The middle dose group delivered 7% fewer pups per litter compared to controls. Pup weight and viability was unaffected as were cumulative days to deliver each litter. Dams in the middle dose group weighed approximately 10% more than controls after the last litter, but otherwise, postpartum body weights were unaffected. The low dose group was apparently unaffected.

The high dose of TCB produced excessive mortality: 19 of 20 females in this group died or were killed for humane reasons during parturition of the first, second, or third litter. Tissues from 8 of these females were taken to determine the cause of death; two had hepatocellular degeneration, one showed signs of lymphoma, and the other causes could not be determined histologically. The males showed transient inactivity and rough hair coat. In the absence of the females, the males were killed and necropsied. A new group of untreated males of the same age was purchased to provide control data. The control males weighed about 5% less than the high dose-treated males, a difference largely attributed to the doubled liver weight in the treated males, compared to controls. The percent abnormal sperm were increased from 10% abnormal forms (control) to 14%. Other organ weight changes were of no biological significance.

Thus, in Task 2, there was significant general and hepatic toxicity but little reproductive toxicity. A Task 3 crossover study was not performed, and the last litter delivered by the controls and lower two dose groups was reared by the dams. While TCB exposure did not reduce pup viability, it produced slight reductions in body weights in the middle dose group, so that by postnatal day 21, body weights were approximately 15% lower than controls.

Task 4 was conducted using control and middle dose mice only because of the minimal reproductive effects seen in Task 2. There were no differences between the controls and the TCB-exposed animals in any reproductive measure. After delivery and evaluation of the F_2 pups, the F_1 adults were killed and necropsied. Male body weights were not affected by TCB exposure, although relative liver weight and kidney weights were increased by approximately 35 and 20%, respectively, while absolute testis weight was increased by approximately 13%. No sperm measures were affected. For females, body weight in the treated animals was increased by approximately 10%, while adjusted liver weight and kidney weight were increased by approximately 38 and 7%, respectively. Estrous cycle length was unchanged. Microscopically, middle dose treated males and females showed greater incidences and severity of hepatic cytomegaly and karyomegaly, and renal tubular regeneration, compared to controls.

Thus, these data show that the hepatic and renal effects of trichloroethylene were significantly greater than the modest reproductive effects observed (reduced pup number, F_0 generation). Clearly, 1,2,4,5-tetrachloro-benzene is not a selective reproductive toxicant, and had no greater effect on the second generation than upon the first in this design.

Summary: NTP Reproductive Assessment by Continuous Breeding Study.

NTIS#: **PB92128388**
Chemical: **1,2,4,5-Tetrachlorobenzene**
CAS#: **95-94-3**
Mode of exposure: **Feed**
Species/strain: **Swiss CD-1 mice**

F_0 generation — Dose concentration →	280 ppm	720 ppm	1800 ppm
General toxicity	Male, female	Male, female	Male, female
Body weight	•, —	•, ↑	↑, —
Kidney weight[a]	•	•	—, •
Liver weight[a]	•	•	↑, •
Mortality	—, —	—, —	—, ↑
Feed consumption	—, —	—, —	•
Water consumption	•	•	•
Clinical signs	—, —	—, —	↑, ↑
Reproductive toxicity			
x̄ litters/pair	—	—	•
# live pups/litter; pup wt./litter	—, —	↓, —	•
Cumulative days to litter	—	—	•
Absolute testis, epididymis weight[a]	•	•	—, ↓
Sex accessory gland weight[a] (prostate, seminal vesicle)	•	•	—, —
Epidid. sperm parameters (#, motility, morphology)	•	•	—, —, ↑
Estrous cycle length	•	•	•

Determination of affected sex (crossover)	Male	Female	Both
Dose level	•	•	•

F_1 generation — Dose concentration →	280 ppm	720 ppm	•
General toxicity	Male, female	Male, female	Male, female
Pup growth to weaning	—, —	↓, ↓	•
Mortality	—, —	—, —	•
Adult body weight	•	—, ↑	•
Kidney weight[a]	•	↑, ↑	•
Liver weight[a]	•	↑, ↑	•
Feed consumption	•	•	•
Water consumption	•	•	•
Clinical signs	•	—, —	•
Reproductive toxicity			
Fertility index	•	—	•
# live pups/litter; pup wt./litter	•	—, —	•
Absolute testis, epididymis weight[a]	•	↑, —	•
Sex accessory gland weight[a] (prostate, seminal vesicle)	•	—, —	•
Epidid. sperm parameters (#, motility, morphology)	•	—, —, —	•
Estrous cycle length	•	—	•

Summary information	
Affected sex?	Unclear
Study confounders:	95% F_0 maternal deaths at 1800 ppm
NOAEL reproductive toxicity:	Not clear
NOAEL general toxicity:	Not clear
F_1 more sensitive than F_0?	No
Postnatal toxicity:	Yes

Legend: —, no change; •, no observation; ↑ or ↓, statistically significant change ($p<0.05$); —, —, no change in males or females. [a]Adjusted for body weight.